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Original Article

Usefulness of natriuresis to predict in-hospital diuretic resistance

Marta Cobo-Marcos[1,2,3], Isabel Zegri-Reiriz[4], Paloma Remior-Perez[1], Sergio Garcia-Gomez[1], Daniel Garcia-Rodriguez[1], Fernando Dominguez-Rodriguez[1,2], Aranzazu Martin-Garcia[5], Pablo Garcia-Pavia[1,2], Javier Segovia-Cubero[1,2]

[1]Department of Cardiology, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain; [2]Centro de Investigación Biomédica en Red en Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain; [3]IDIPHSA, Madrid, Spain; [4]Department of Cardiology, Heart Failure and Transplant Unit, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [5]Department of Laboratory of Biochemistry-Clinical Analysis, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain

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Abstract: Background: Urinary sodium excretion predicts long-term adverse events after discharge in patients with acute heart failure (AHF). The role of natriuresis as an early marker of poor diuretic response during an AHF episode has been scarcely investigated. We sought to evaluate whether early natriuresis or its change during heart failure hospitalization is associated with the development of in-hospital diuretic resistance (DR). Methods: This was a prospective, observational single center study of consecutive patients with AHF. Urine electrolytes were estimated from a spot urine sample within the first 6 hours following the first diuretic dose and 48 hours after admission. In-hospital DR was defined as poor diuretic response based on diuretic efficiency metrics and persistent congestion despite an intensive diuretic protocol. Results: Between January and December 2018, 143 patients were admitted for AHF. Of these, 102 fulfilled the inclusion criteria (60% males, median age 77 years [interquartile range [IQR]: 69-83), and 20 patients (19.6%) met the definition of DR. Early natriuresis was lower in patients with DR than in non-resistant patients (46 mEq/L [IQR: 38.5-80.0] vs 97.5 mEq/L [IQR: 70.5-113.5], P<0.001). Urinary sodium <50 mEq/L increased the risk of developing in-hospital DR (risk ratio: 5.011 [95% confidence interval 2.408-10.429], P<0.001). The area under the receiver operating characteristic curve for early natriuresis to predict DR was 0.791 (95% confidence interval 0.681-0.902, P<0.001). Conclusions: Initial natriuresis can predict in-hospital DR. Patients with urinary sodium <50 mEq/L have an increased risk of early resistance to diuretic treatment.

Keywords: Diuretic resistance, natriuresis, heart failure

Introduction

In a recent position statement by the European Society for Cardiology, diuretic resistance (DR) is defined as an "impaired sensitivity to diuretics resulting in reduced natriuresis and diuresis limiting the possibility to achieve euvolemia" [1].

The identification of patients with DR is one of the most important challenges in the field of heart failure (HF), as DR is associated with a higher risk of re-hospitalization and increased mortality [2-7]. At present, no uniform and standard definition is available to identify patients at risk of developing resistance to diuretic treatment, especially during HF hospitalization. The early identification of these patients could allow the intensification of treatment and may improve symptoms and decrease the length of hospital stay.

Sodium and fluid retention is a hallmark of HF [8, 9]. As effective diuretic response is produced by natriuresis, urinary sodium has emerged as a useful parameter to predict natriuretic response in patients with HF soon after diuretic administration, which can be measured from a urinary spot sample with good accuracy [10]. In this line, several studies have reported the usefulness of natriuresis after the first dose of diuretic to predict long-term adverse events

in patients with acute HF (AHF) after discharge [10-15]. However, the role of urinary sodium as an early marker of poor diuretic response during an AHF episode has been scarcely investigated [16].

The aim of this study was to examine whether basal natriuresis and/or its change during an AHF episode is associated with the development of in-hospital DR in patients admitted for HF.

Methods

From January to December 2018, we conducted a prospective, observational and single center study on a sample of consecutive patients aged ≥18 years whose primary admission diagnosis was AHF. Patients in cardiogenic shock (or requiring vasoactive support) and/or on dialysis were excluded. Patients in whom weight, urine output, or natriuresis could not be recorded or were missed were also excluded.

The present study conforms to the principles of the Declaration of Helsinki. Approval from the local ethics committee/internal review board was obtained at the participating centers and patients signed an informed consent.

Definition of in-hospital diuretic resistance

In-hospital DR was defined as persistent congestion signs evaluated with the EVEREST scale [17], in addition to poor diuretic response determined by weight-based diuretic efficiency parameters, and after a pre-specified and intensive diuretic protocol. Diuretic efficacy parameters are based on the weight difference per 40 mg of intravenous or oral equivalent administered furosemide (Δ weight kg/[(total intravenous dose)/40 mg]) [4-7]. They were evaluated 48 hours after the admission and daily afterwards. Diuretic response was considered poor if congestion persisted and diuretic efficacy by weight was lower than 0.2 kg/40 mg of furosemide, a threshold based on previous published studies [4-7]. The diuretic protocol included 48 hours of furosemide perfusion (daily dose superior to 240 mg) and a thiazide, based on the *Cardiorenal Rescue Study in Acute Decompensated Heart Failure* (CARRESS-HF) trial protocol [18].

Study procedures and statistical analysis

A spot urinary sample was taken within 6 hours of the first diuretic administration in the emergency room, and on the morning of the third day of admission after the diuretic. Urine sodium was measured using a Siemens Dimension EXL chemistry analyzer. Baseline characteristics, physical examination, diuresis, diuretic treatment and laboratory data were assessed daily. Values of continuous variables are given as the median and interquartile range (IQR). Categorical variables are described in absolute and relative frequencies. The area under the receiver operating characteristic curve (AUC) was used to evaluate the accuracy of the use of natriuresis level to estimate DR. The associations between clinical characteristics and natriuresis on admission and after 48 hours, and DR, were analyzed by univariate analysis using the Chi square test for categorical variables and the Mann-Whitney U test for contiuous variables. A *p*-value <0.05 was considered significant. All analyses were performed using STATA v.13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX) and R software (R Foundation for Statistical Computing, version 3.6.0).

Results

Between January and December 2018, 143 patients were admitted for AHF. Of these, 102 patients fulfilled the inclusion criteria (60% males, median age 77 years [IQR: 69-83], 42.5% with left ventricle ejection fraction <50%).

Twenty patients (19.6%) met the definition of DR. These patients had lower early natriuresis than non-resistant patients (46 mEq/L [IQR: 38.5-80.0] *vs* 97.5 mEq/L [IQR: 70.5-113.5], P<0.001]. Urinary sodium <50 mEq/L increased the risk of developing in-hospital DR (risk ratio: 5.011 [95% confidence interval 2.408-10.429], P<0.001).

The AUC for early natriuresis to predict DR was 0.791 (95% confidence interval: 0.681-0.902), P<0.001) (**Figure 1**). Urinary sodium <50 mEq/L had 88% sensitivity and 55% specificity to detect patients with DR.

After 48 hours of diuretic treatment, the natriuresis response declined in both groups and was not associated with DR (60 mEq [IQR: 20-92.5] in DR *vs* 63 mEq (IQR: 35.5-83.5) in non-resistant, P=0.298).

Neither the diuretic response by weight nor the diuresis adjusted for furosemide on the first 48

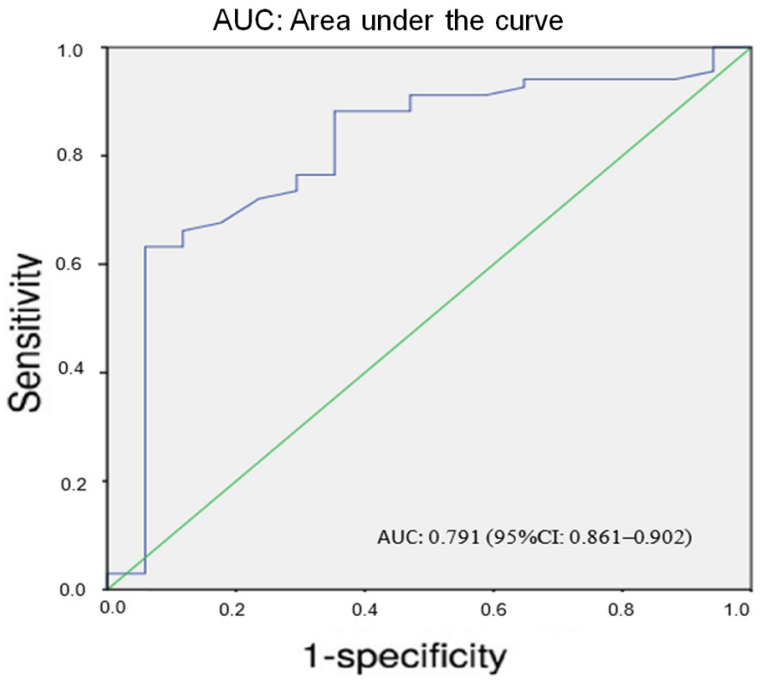

Figure 1. Receiver operating characteristic curve for urinary sodium after diuretic administration to discriminate between patients with and without diuretic resistance.

hours were predictors of in-hospital poor diuretic response (**Table 1**).

Characteristics of patients with in-hospital diuretic resistance

Compared with non-resistant patients, those with DR had a higher proportion of chronic renal failure, with significantly worse glomerular filtration rate (P=0.033) and higher levels of plasma urea (P<0.01). Basal furosemide oral dose treatment was also higher in this group (P<0.001). On admission, patients with DR presented with more right congestion signs and significantly lower hemoglobin levels (P< 0.001). Left ventricular ejection fraction and NT-proBNP levels were not statistically different between the groups (**Table 1**).

During the first 48 hours, patients with DR received a higher furosemide dose (240 [IQR: 240-320] *vs* 200 [IQR: 160-240] mg, P=0.004), more often required the combination with other diuretics (35% *vs* 13%, P=0.023), and had a longer hospital stay (23 [IQR: 15-36] *vs* 7 [IQR: 6-11] days, P<0.001) than non-resistant patients (**Table 2**).

Discussion

The present study shows that early natriuresis can predict in-hospital DR in patients with AHF. We also show that patients with urinary sodium <50 mEq/l have an increased risk of early resistance to diuretic treatment, indicating the need for intensifying diuretics and longer hospitalization.

Definition of diuretic resistance

One limitation on research into DR is the lack of a standard definition of refractory congestion. In the present study, DR was prospectively assessed along the entire admission process, and was based on diuretic efficacy parameters. Diuretic efficacy by weight correlates better with the occurrence of adverse events than does weight loss, diuresis or diuretic dose in isolation [4-7]. Accordingly, our goal was to derive objective and reproducible parameters considering the absolute weight loss together with the administered diuretic dose. Diuretic treatment was also pre-specified and all patients with DR had previously received an intensive treatment that included 48 hours of a combination of furosemide and a thiazide, according to the stepped pharmacologic protocol previously used in the CARRESS-HF trial [18]. Based on this, almost 20% of patients with AHF in our study showed DR. These patients presented with a more advanced disease and comorbidities. None of these baseline characteristics are generally used in clinical practice to guide diuretic treatment. In addition, neither the weight change nor the initial diuresis was associated with the development of in-hospital diuretic resistance in our study.

Natriuresis and diuretic resistance

Several studies have highlighted the prognostic value of natriuresis in different HF scenarios [10-15, 19-21], but few have evaluated the association between natriuresis and in-hospital DR. Collins et al. found that a low urine sodium (<35.4 mmol) one hour after diuretic therapy was suggestive of the development of worsening HF [16]. Worsening HF was defined as the need for escalation of diuretics or administration of intravenous vasoactives during the first

Table 1. Baseline characteristics per diuretic response

	All patients n=102	Diuretic resistance n=20 (19.6%)	No diuretic resistance n=82 (80.4%)	*p*-value
Age* (years)	76.6 (69.7-82.8)	80.5 (66.3-83.4)	76.2 (69.7-82.4)	0.614
Male, n (%)	61 (59.8)	11 (55)	50 (61)	0.436
Diabetes mellitus 2, n (%)	47 (46.1)	10 (50)	37 (45)	0.695
Arterial hypertension, n (%)	78 (76.5)	16 (80)	62 (76)	0.678
Chronic kidney disease, n (%)	26 (25.5)	9 (45)	17 (21)	0.026
Ambulatory furosemide* (mg)	20 (0-40)	60 (30-80)	20 (0-40)	<0.001
LVEF (%)	53 (35-60)	50 (35.7-60)	53 (35-60)	0.928
TAPSE* (mm)	17 (15-20)	17 (15.5-19)	17 (14-22)	0.815
Systolic blood pressure (mmHg)*	127.5 (110-140)	126.5 (120-135)	127.5 (110-148)	0.572
Diastolic blood pressure (mmHg)*	68 (60-80)	62 (55-74)	68.5 (60-80)	0.127
Edema ≥2, n (%)	33 (33)	11 (55)	22 (27)	0.01
Inferior cava vein (mm)	22 (18-25)	23 (21-30)	22 (18-24)	0.067
Blood tests				
Glomerular filtration ml/min/1.73 m^2*	60.2 (37.3-81.6)	39.6 (22.5-74.9)	61.4 (39.5-82)	0.033
Urea (mg/dl)*	64 (46.5-100.5)	104.5 (59.7-173.7)	58 (46-91.5)	0.01
Sodium (mmol/l)*	140 (138-143)	140 (134.7-142.5)	141 (138-143)	0.255
Potassium (mmol/l)*	4.3 (4-4.7)	4.5 (4.1-4.7)	4.3 (3.9-4.6)	0.214
Chloride (mmol/l)*	104 (101-106)	103 (98-105)	104 (102-106)	0.140
NT-proBNP (pg/ml)*	4159 (2363-8362)	3896 (1227-7537.7)	4654 (2619-8477)	0.299
Uric acid (g/dl)*	8.6 (7.1-10.4)	8.4 (7-10.4)	8.6 (7.2-10.4)	0.903
Hemoglobin (g/dl)*	12.1 (10.8-14.3)	10.5 (9.2-12.5)	12.5 (11.2-14.4)	0.001
Albumin (g/dl)*	3.8 (3.5-4)	3.7 (3.4-4)	3.9 (3.5-4.1)	0.160
Urinary parameters				
UNa (mEq)*	87 (61.7-113)	46 (38.5-80.0)	97.5 (70.5-113.5)	<0.001
UNa <50 mEq, n (%)	20 (19.6)	11 (55)	9 (11)	<0.001
UK (mEq)*	27.5 (20.6-39.5)	39.9 (28-54.8)	25.7 (19-35)	0.001
UCl (mEq)*	108.5 (87-125)	89.5 (63.2-101.5)	116 (94.7-129)	0.03
UCr (mEq)*	34.9 (17.1-60.7)	43 (20-65.3)	32 (15.2-57.9)	0.381
FENa (%)	2.1 (0.9-5.2)	1.5 (0.7-4.2)	2.5 (0.8-5.6)	0.185
UNa/K*	3.1 (1.5-5.1)	1.4 (0.7-2.2)	3.7 (2-6.2)	<0.001
UNa/K <1, n (%)	14 (13.7)	7 (35)	7 (8.5)	0.002
UNa day 3 (mEq)*	63 (34-85)	60 (20-92.5)	63 (34.7-83.2)	0.545

LVEF: left ventricular ejection fraction; TAPSE: tricuspid annular plane systolic excursion; NTproBNP: N-terminal pro-brain natriuretic peptide; UNa: urinary sodium; UK: urinary potassium; UCl: urinary chloride; UCr: urinary creatinine; FENa: fractional excretion of sodium. *Continous variables are expressed by medians and interquartile range.

five days of admission. Despite the different definitions of DR used, the proportion of patients who developed in-hospital DR and the main findings were similar in the Collins et al. study and our present study. Accordingly, our findings reinforce the value of initial natriuresis as a useful biomarker to predict early DR.

Limitations

Our cohort consisted of 102 patients from one academic institution and so our findings may not be generalizable to the wider AHF population. The percentage of patients who developed in-hospital diuretic resistance was 19.6%, and so the total number of events (n=20) was small. There is an absence of specific criteria to define in-hospital diuretic resistance, but in the present study it was based on previous published reports and specified protocols.

Conclusions

Initial natriuresis can predict in-hospital DR in AHF. Patients with urinary sodium <50 mEq/L have an increased risk of early resistance to diuretic treatment. This finding can help to

Table 2. Treatment outcomes and diuretic response in DR and non-DR patients

	All patients n=102	Diuretic resistance n=20 (19.6%)	No diuretic resistance n=82 (80.4%)	*p*-value
Treatment				
Furosemide mg (48 hours)*	240 (160-240)	240 (240-320)	200 (160-240)	0.004
Diuretic association (%)	18 (17.6)	7 (35)	11 (13.4)	0.023
Length of stay (days)*	9 (6-15)	23 (15-36)	7 (6-11)	<0.001
Diuretic response (48 hours)				
Weight*	-0.33 (-0.66, -0.19)	-0.2 (-0.71, -0.07)	-0.36 (-0.6, -0.2)	0.268
Diuresis*	631 (497-897)	688 (441-848)	626 (506-910)	0.942

*Continous variables are expressed by medians and interquartile range.

stratify patients who may benefit from a more intense treatment for decongestion during hospital admission.

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Disclosure of conflict of interest

None.

Address correspondence to: Marta Cobo-Marcos, Centro de Investigación Biomédica en Red en Enfermedades Cardiovasculares, C/Manuel de Falla 1, 28222, Majadahonda, Madrid, Spain. Tel: 0034-676743454; E-mail: martacobomarcos@hotmail.com

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